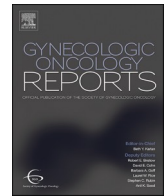




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The association of talc use and ovarian cancer: biased or causal

In a recent review published in *Gynecologic Oncology* (Wentzensen and O'Brien, 2021), Wentzensen and O'Brien summarized epidemiologic evidence on the association between genital talc use and ovarian cancer. They noted that retrospective case-control studies have shown associations between genital powder use and ovarian cancer with summary relative risk estimates from 1.24 to 1.35. In contrast, prospective cohort studies have not shown a statistically significant association between genital powder use and ovarian cancer until recently when a pooled analysis (O'Brien et al., 2020) of four large cohorts "demonstrated a weak, but statistically significant association among women with patent reproductive tracts (hazard ratio 1.13)." This opinion, I think correctly, departs from that expressed in an editorial accompanying the pooled analysis paper (Gossett and Del Carmen, 2020) which concluded that only the "statistically unsophisticated" would selectively highlight the positive finding in women with intact genital tracts when the overall HR of 1.08 with a lower confidence limit of 0.99 missed statistical significance. Wentzensen and O'Brien's conclusion that the pooled study does suggest a significant association is also at odds with National Cancer Institute (NCI)'s PDQ advice to patients on prevention of ovarian cancer (PDQ for Patients) which, as recently as 8/23/2021, dismissed the talc association with the single sentence: "Studies of women who used talcum powder (talc) dusted on the perineum (the area between the vagina and the anus) have not found clear evidence of an increased risk of ovarian cancer." Although the PDQ Editorial Board, responsible for this opinion, is independent of NCI, most women would likely interpret this as the Institute's official position.

Wentzensen and O'Brien do point out the possibility of preferential recall of exposure by cases in case-control studies. They highlight a case-control study of ovarian cancer in African American women in whom exposure to talc was assessed by interviews—some conducted before 2014 and some after 2014 when there might have been greater awareness of the talc association (Schildkraut et al., 2016). Pre-2014 compared to post-2014, "any genital use" increased in cases from 36.5% to 51.5% while any genital use for controls stayed about the same—34.0% vs. 34.4%. While interpreted as evidence of recall bias, I believe it is debatable whether genital talc use was *erroneously under-reported* by cases before 2014 as opposed to *erroneously over-reported* in cases after 2014. In our 2016 paper (Cramer et al., 2016), we found that 54% of African American cases reported genital talc use compared to 26% of African American controls. These data came from interviews conducted prior to 2014. In a larger study of ovarian cancer in African American women, again conducted before 2014, Wu et al. reported 48% of cases reported talc use which is above the pre-2014 exposure rate of 36.5% (Wu et al., 2015). Also, it is not clear to me why recall bias should be selective and account for positive associations for serous cancer but null associations for mucinous cancers—differences in the association by histology pointed out by the reviewers (Wentzensen and O'Brien, 2021).

Another bias is confounding which can occur when an underlying cause of the outcome also causes changes to exposure. The authors propose that: "An example relevant to the powder-ovarian cancer association is if a hormone-related condition was a risk factor for ovarian cancer and, also, altered the vaginal environment in a way that made women more or less likely to apply genital powder." If true, this should have led to a spurious association in the cohort studies as well; nor is clear what that "hormone related condition" is and how it could be adjusted for.

In their conclusion, the authors express doubt that the observed associations are causal and note that "given the widespread use of powder and the rarity of ovarian cancer, the case for public health relevance is limited." Limited relevance does not seem a good descriptor of Wu et al.'s estimate that talc use for greater than 1 year was associated with a population attributable risk of 12.2–15.1% for ovarian cancer (Wu et al., 2015). Regarding causality, a fully informed opinion about this should have included a review of recent experimental studies including one by Fletcher et al. who exposed human ovarian cancer cells and normal fallopian tube cells to talc and found significant increases in markers of inflammation and cell proliferation to a greater degree in the normal compared to the cancer cells (Fletcher et al., 2019). Talc exposure also resulted in production of the ovarian cancer tumor marker, CA125, by cells. Another important study looked at effects of the combination of estradiol and talc on macrophages (Mandarino et al., 2020). This study revealed that the talc and estrogen-exposed macrophages produced reactive oxygen species and changes in macrophage genes pertinent to cancer development and immunosurveillance. When the treated macrophages were co-cultured with murine ovarian surface epithelial cells, proliferation of the epithelial cells was observed. These effects were not seen with titanium dioxide and estradiol. The apparent synergistic effect of estradiol with talc provides a biologic basis for our observation that postmenopausal women using estrogen replacement had greater risk for a ovarian cancer with talc use than postmenopausal women who had used talc but hadn't taken hormone replacement.

I end by noting that the entire body of evidence, both epidemiologic and experimental, was exhaustively reviewed by Health Canada, the Canadian equivalent of the Federal Drug Administration (Environment and Climate Change Canada Health Canada, 2021). They conclude:

'With regards to perineal exposure, analyses of the available human studies in the peer reviewed literature indicate a consistent and statistically significant positive association between perineal exposure to talc and ovarian cancer. The available data are indicative of a causal effect. Given that there is potential for perineal exposure to talc from the use of certain self-care products (e.g., body powder, baby powder, diaper and rash creams, genital antiperspirants and deodorants, body wipes, bath bombs, bubble bath), a potential concern for human health has been identified.'

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Presumably, this report was not available for review by Wentzensen and O'Brien before they completed their report but would seem to require their response at this time about causality and public health relevance of the association between genital use of talc and ovarian cancer.

Author contribution

Dr. Cramer is solely responsible for the content of the correspondence.

Declaration of Competing Interest

The author declares the following financial interests/personal relationships which may be considered as potential competing interests: Dr. Cramer reports being a paid witness for the plaintiff in litigation related to talc and ovarian cancer.

References

- Environment and Climate Change Canada Health Canada, 2021. Chemical Abstracts Service Registry Number 14807-96-6. Government of Canada.
- Cramer, D.W., Vitonis, A.F., Terry, K.L., Welch, W.R., Titus, L.J., 2016. The association between talc use and ovarian cancer: A retrospective case-control study in two US states. *Epidemiology* 27, 334–346. <https://doi.org/10.1097/EDE.0000000000000434>.
- Fletcher, N.M., Harper, A.K., Memaj, I., Fan, R., Morris, R.T., Saed, G.M., 2019. Molecular basis supporting the association of talc powder use with increased risk of ovarian cancer. *Reprod. Sci.* 26 (12), 1603–1612.

- Gossett, D.R., Del Carmen, M.G., 2020. Use of powder in the genital area and ovarian cancer risk: examining the evidence. *JAMA* 323 (1), 29–31.
- Mandarino, A., Gregory, D.J., McGuire, C.C., Leblanc, B.W., Witt, H., Rivera, L.M., Godleski, J.J., Fedulov, A.V., 2020. The effect of talc particles on phagocytes in coculture with ovarian cancer cells. *Environ. Res.* 180, 108676. <https://doi.org/10.1016/j.envres.2019.108676>.
- O'Brien, K.M., Tworoger, S.S., Harris, H.R., Anderson, G.L., Weinberg, C.R., Trabert, B., Kaunitz, A.M., D'Aloisio, A.A., Sandler, D.P., Wentzensen, N., 2020. Association of powder use in the genital area with risk of ovarian cancer. *JAMA* 323 (1), 49. <https://doi.org/10.1001/jama.2019.20079>.
- PDQ for Patients. Available from: <https://www.cancer.gov/types/ovarian/patient/ovarian-prevention-pdq>.
- Schildkraut, J.M., Abbott, S.E., Alberg, A.J., Bandera, E.V., Barnholtz-Sloan, J.S., Bondy, M.L., Cote, M.L., Funkhouser, E., Peres, L.C., Peters, E.S., Schwartz, A.G., Terry, P., Crankshaw, S., Camacho, F., Wang, F., Moorman, P.G., 2016. Association between body powder use and ovarian cancer: the African American Cancer Epidemiology Study (AACES). *Cancer Epidemiol. Biomarkers Prev.* 25 (10), 1411–1417.
- Wentzensen, N., O'Brien, K.M., 2021. Talc, body powder, and ovarian cancer: a summary of the epidemiologic evidence. *Gynecol. Oncol.* 163 (1), 199–208.
- Wu, A.H., Pearce, C.L., Tseng, C.-C., Pike, M.C., 2015. African Americans and Hispanics Remain at lower risk of ovarian cancer than non-hispanic whites after considering nongenetic risk factors and oophorectomy rates. *Cancer Epidemiol. Biomarkers Prevent.* 24 (7), 1094–1100.

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